BMJ Open Nocturnal antihypertensive treatment in patients with type 1 diabetes with autonomic neuropathy and non-dipping of blood pressure during night time: protocol for a randomised, placebo-controlled, double-blind, two-way crossover study

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ABSTRACT

Introduction: Cardiac autonomic neuropathy (CAN) and elevated nocturnal blood pressure are independent risk factors for cardiovascular disease in patients with diabetes. Previously, associations between CAN, non-dipping of nocturnal blood pressure and coronary artery calcification have been demonstrated. The present protocol describes a trial to test the efficacy of bedtime dosing of the ACE inhibitor enalapril on night time blood pressure and left ventricular mass in patients with type 1 diabetes.

Materials and methods: In a randomised, double-blind, two-way cross-over study, 24 normoalbuminuric patients with type 1 diabetes with CAN will be treated for 12 weeks with either morning or bedtime dosing of 20 mg enalapril, followed by 12 weeks of switched treatment regimen. During each treatment period, two 24 h ambulatory blood pressure measurements will be performed and after each treatment period left ventricular mass will be determined by multisliced CT. Primary end points will be reduction in blood pressure and reduction in left ventricular mass.

Ethics and dissemination: The study has been approved by the Danish Medicines Agency, the Scientific-Ethical Committee of the Capital Region of Denmark and the Danish Data Protection Agency. An external monitoring committee (the Good Clinical Practice Unit at Copenhagen University Hospital) will oversee the study. The results of the study will be presented at national and international scientific meetings and publications will be submitted to peer-reviewed journals.

Trial registration number: EudraCT (2012-002136-90).

INTRODUCTION

The pathogenesis of hypertension in patients with type 1 diabetes comprises substantial

vessel wall pathology. A number of observations suggest, however, that cardiac autonomic neuropathy (CAN) may also play a role in the development of hypertension.¹

The normal diurnal variability in blood pressure includes a decline in blood pressure during the night and a reduction in heart frequency. The primary cause of reduced heart frequency and the supposed decline in blood pressure is an increased vagal tone during the night.² CAN affecting vagal nerve function is a frequent and early complication in patients with type 1 diabetes and may play a role in the smaller reduction in heart frequency and thereby the less decline than normal in blood pressure during the night in patients with neuropathy.³

Associations between CAN and less decline in blood pressure during the night have been described in a number of observations^{1 4-8} and the condition is encumbered with considerable increased morbidity and mortality.⁹⁻¹⁴ In a recent study we have shown a relation between CAN, reduced diurnal variability in blood pressure and increased left ventricular mass. Whether this relationship is of importance for the increased morbidity and mortality in patients with CAN is at the moment unclear.¹⁵

Previous studies in patients with essential hypertension have suggested that patients with reduced diurnal variation in blood pressure will reduce their night time blood pressure by taking antihypertensive treatment at bedtime.¹⁶ Pharmacological treatment of hypertension can possibly, on its own,

improve autonomic dysfunction.¹⁷ Heart rate variability was increased in a short study of ACE inhibitors in patients with type 1 diabetes.¹⁸ However, no studies on pharmacologically re-establishing the normal diurnal variation in blood pressure in type 1 diabetes have been published despite the request for such a study.¹⁹

The first-line choice for treatment of hypertension in type 1 diabetes is ACE inhibition. The recommended standard dose of enalapril is 20 mg once daily given in the morning. The maximal antihypertensive effect of the drug is seen after 4–6 h with diminishing but still present effect on blood pressure for 24 h. Thus, theoretically, the drug should be ideal for re-establishing the normal diurnal blood pressure variation if given at bedtime.

In the following, a protocol for the investigation of the efficacy of nocturnal antihypertensive treatment in patients with type 1 diabetes and isolated autonomic neuropathy including background knowledge, experimental design and planned analyses will be described.

PROGNOSIS AND PRESENT TREATMENT OF AUTONOMIC DIABETIC NEUROPATHY

CAN is a severe complication to diabetes, and is associated with increased morbidity and mortality.¹² CAN rarely exists as an isolated complication to diabetes.¹⁰ Furthermore, the mechanisms by which CAN may increase the risk of cardiovascular disease is unknown but factors such as exercise intolerance,²⁰ silent myocardial infarction²¹ and arrhythmias²² have been proposed.

Although specific treatment of the condition does not exist, improvement of glycaemic control can slow the progression of CAN,²³ and symptomatic treatment with ACE inhibitors and β -blockers is available.²⁴

Recently, it has been demonstrated that targeting nocturnal hypertension in patients with type 2 diabetes by bedtime dosing of antihypertensive medications is able to reduce night time blood pressure significantly,²⁵ and in a large open-labelled study in type 2 diabetes, Hermida *et al*²⁶ have demonstrated reduced cardiovascular morbidity and mortality when antihypertensive medication was prescribed at bedtime.

In a previous cross-sectional study of patients with long-term type 1 diabetes with isolated CAN, we found a close relation between CAN, elevated night time blood pressure and non-dipping of blood pressure during the night.¹⁵ On the assumption that these factors possibly are caused by increased sympathetic modulation during the night, the present study is designed to elucidate whether night time antihypertensive treatment with an ACE inhibitor, enalapril, in comparison with morning dosing of enalapril is superior in reducing night-time blood pressure and the frequency of non-dipping of blood pressure during night. Moreover, left ventricular mass measured by multisliced CT (MSCT) scan may illustrate if reduced night time blood pressure will be reflected in reduced left ventricular mass.

OBJECTIVE

The primary objective is to evaluate the effect of treatment with enalapril 20 mg given at bedtime compared with enalapril 20 mg given in the morning on mean arterial blood pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP) and per cent dipping in SBP during night.

The secondary objective is to evaluate the effect of night or day time dosing of enalapril on left ventricular mass measured by MSCT scan.

METHODS/DESIGN

Design

The study is an investigator-initiated, prospective, randomised, placebo-controlled, double-blind cross-over study of 24 weeks duration investigating the effect of enalapril 20 mg given at bedtime or in the morning on diurnal blood pressure. The patients will be randomised to take enalapril 20 mg in the morning and identical tablets with placebo at bedtime or enalapril 20 at bedtime and placebo in the morning in random order.

We have prepared 30 sets of medicine, each containing a box with placebo and a box with active medicine. Participants are randomised in blocks of 10 to receive either enalapril or placebo in the first 12 weeks and the opposite in the next 12 weeks. The allocation sequence is generated by the chemist at the dispenser and the medicine box sets are numbered from 101 to 130. The participants will be enrolled by the study nurse and the patients are assigned prospectively to treatment from 101 to 130. Active medicine and placebo are both produced in gelatine-coated capsules of similar taste and appearance. Patients, study nurse, investigators and laboratory technicians are all blinded to the treatment.

Recruitment will proceed until 24 participants have completed 12 weeks of treatment. Participants who withdraw, drop out or are excluded will be replaced to ensure 24 fulfilled patients. Participants and investigators will be blinded for allocated treatment and kept masked until last patient or last visit.

If patients are not treated with antihypertensive medication prior to the screening, 10 mg of enalapril is given in the morning for 4 weeks, assuring the medication is tolerated before randomisation to study medication. Patients already treated with ACE inhibitors or angiotensin 2 receptor blockers will discontinue this treatment when the study medication is given. All other antihypertensive drugs will be prescribed unchanged, and we intend not to intervene with present glycaemic control or daily clinical practise.

Participants

Patients with long-term type 1 diabetes and CAN defined as two or more abnormal autonomic function tests³: heart rate variability during deep breathing, Valsalva ratio, lying-to-standing test and blood pressure response to standing up, and a reduced diurnal variation

in blood pressure, will be recruited from the outpatient clinic cohort of patients with type 1 diabetes at the Diabetes Unit, Rigshospitalet and Steno Diabetes Center.

The inclusion criterion will be type 1 diabetes according to WHO/ADA Criteria, age between 18 and 75 years, glycosylated haemoglobin below 10% (86 mmol/mol), normal urinary albumin excretion and no clinical signs of cardiovascular disease. Exclusion criteria are urinary albumin excretion rate above 30 mg/24 h, serum creatinine above 120 µmol/L, renal artery stenosis or other known kidney disease, myocardial infarction or coronary revascularisation, transient ischaemic attack or stroke, known side effects to or contraindication for treatment with ACE inhibitors, or known malignant diseases.

The criteria for discontinuing the study are unacceptable side effects of the study drug, withdrawal of informed consent or pregnancy. We have not planned to modify the intervention. If side effects appear during the study period, the study drug will be discontinued.

Inclusion and exclusion criteria are presented in boxes 1 and 2.

EXPERIMENTAL DESIGN

Suitable patients will be approached by telephone contact by one of the investigators (TJ) and by receiving a letter with study information. Interested patients are invited to screening at the hospital. The patients will again receive detailed oral and written information before consent is obtained. Thereafter, the screening procedures will be performed. All participants will follow the same study plan with an initial screening visit followed by an intervention period of 24 weeks. An outline of the trial visits and examinations is shown in table 1.

Trial visits and examinations

At the screening visit weight and height are measured without shoes. A 12-lead ECG is then recorded.

CAN tests

For determination of heart rate variability the patients are asked to breathe deeply at a rate of 6 breaths/minute while being monitored on a (50 mm/s) 12-lead ECG. The maximum and minimum heart rates during

Box 1 Inclusion criteria

Male or female; aged 18–75 years;
Type 1 diabetes according to WHO/ADA criteria;
Presence of cardiovascular autonomic neuropathy defined as two or more abnormal autonomic function test;
Reduced diurnal variation in blood pressure (<10%);
Glycosylated haemoglobin <10% (<86 mmol/mol);
Normal urinary albumin excretion rate (<30 mg/24 h);
No clinical signs of cardiovascular disease.

Box 2 Exclusion criteria

Type 2 diabetes;
Known side effects such as angio-oedema to ACE-inhibitor treatment;
Cancer or any other clinically significant disorder, which in the investigator's opinion could interfere with the results of the trial;
Elevated urinary albumin excretion rate (>30 mg/24 h);
Serum creatinine above 120 µmol/L;
Known renal artery stenosis or known kidney disease;
Previous myocardial infarction or coronary revascularisation, transient ischaemic attack or stroke;
Known or suspected abuse of alcohol or narcotics.

each breathing cycle are measured, and the mean difference of six cycles will be calculated. Abnormal values are differences below 10 bpm. The lying-to-standing heart rate ratio is determined after at least 5 min rest in the supine position and the maximal-to-minimal heart rate ratio is calculated from the R-R interval measured after the 30th beat after standing up, to the R-R interval measured after the 15th beat after standing up. An abnormal value will be a ratio below or equal to 1. The Valsalva test consists of forced exhalation into a mouthpiece with a pressure of 40 mm Hg for 15 s, and the ratio of the maximum to the minimum R-R interval during the test is calculated. The test is performed three times, and the mean value of the ratios is used. Abnormal values will be ratios below or equal to 1.10. Orthostatic hypertension is defined as decrease in SBP of 30 mm Hg when changing from supine to the upright position.

Ambulatory 24 h blood pressure recording

Measurements are performed on the non-dominant arm with a properly calibrated Blood Pressure Monitor System 90217 from Space Laboratories (Washington DC). The SBP, DBP and heart rate are measured automatically every 20 min during daytime (between 0600 and 2200 h) and once every hour during night time (between 2200 and 0600 h) for 24 consecutive hours. Blood pressure will be validated within 2 days after delivery and measurements are not considered valid if >30% of the measurements are missing, or if not at least 20 measurements during daytime and at least 7 measurements during night time are obtained. In these cases, the measurements will be repeated immediately to ensure a sufficient number of measurements.

Blood samples will be collected, medical history will be recorded and a full physical examination will be performed. All female participants of childbearing potential will be tested for pregnancy and assurance will be obtained of adequate use of contraceptive methods throughout the study period.

Data from each patient will be collected and entered consecutively for each patient. Twenty-four hour blood pressure profiles and MSCT results will be transformed to paper format and will, together with laboratory data,

Table 1 Trial visits and examinations

Visit	1	2	3	4	5	6	7
Week	0	6	11	12	18	23	24
Informed consent	X						
Screening and randomisation	X						
Physical examination	X						
Blood samples*	X		X			X	
Dispensing of trial medication	X		X				
Adverse event assessment		X	X	X	X	X	X
24 h blood pressure recording		X	X		X	X	
Heart-MSCT				X			X

*Glycosylated haemoglobin, serum creatinine and NT-proBNP.
Heart MSCT, cardiac multisliced CT.

be kept at a laboratory behind locked double doors. Data will be destroyed 10 years after the end of the study.

During the intervention period, all participants will attend seven planned visits: randomisation (week 0), week 6, week 11, week 12, week 18, week 23 and week 24. At weeks 0, 11 and 23, blood samples will be collected and trial medication will be dispensed. At visits 1–7, used packaging will be collected to estimate compliance, adverse events will be assessed and glycaemic control will be evaluated. To encourage adherence, the participants can come to the visits when they wish (choice of weekday, time of day, etc). A 24 h telephone service is available to all patients.

At weeks 6, 11, 18 and 23, ambulatory 24 h blood pressure recordings will be performed.

At the end of each of the two study periods (at weeks 12 and 24), MSCT (Toshiba Aquillon One 320 volume) will be performed measuring ventricular mass and volume, coronary artery stenosis and coronary calcium score.

The study will be carried out under the surveillance and guidance of the Good Clinical Practice (GCP) Unit at Copenhagen University Hospital in compliance with the ICH-GCP guidelines.

The security of the patients will be supervised by blood sample control at the start and the end of the study. We recommend observation and reporting of symptoms and possible side effects in the patients' diaries or by use of the 24 h telephone service to the study staff.

Intervention

Trial medication will be initiated on the randomisation day in a dosage of enalapril 20 mg given in the morning or at bedtime and identical placebo tablets given in the morning and at bedtime. In patients not taking ACE inhibitors before entrance into the study, a dose of enalapril 10 mg in the morning is given for 4 weeks to ensure tolerability of the drug. Thereafter, these patients are randomised to enalapril 20 mg given in the morning

or at bedtime. Patients already in treatment with ACE inhibitors or ATII blockers will discontinue this treatment when entering the study. All other antihypertensive medication will be prescribed unchanged.

END POINT MEASURES

The primary end point is to evaluate the effect of treatment with enalapril 20 mg given at bedtime compared with enalapril 20 mg given in the morning on MAP, SBP, DBP and per cent dipping in MAP during night. The calculations will be based on both 24 h blood pressure readings in each treatment period.

The secondary end point is left ventricular volume and left ventricular mass measured by MSCT at the end of each treatment period.

POWER CALCULATION AND STATISTICS

The cross-over design makes it possible to compare the two treatment modalities within the same person thereby minimising between-patient variation.

By setting power to 80%, a test level of 5% and a SD of 5 mm Hg on blood pressure measurements, a sample size of 24 patients will be sufficient to detect a difference of 4 mm Hg between the two treatment modalities.

The results will be expressed as means and SD when values are normally distributed and as medians and IQR when the values are not normally distributed. Paired Student t tests will be used when the values are skewed; otherwise Wilcoxon tests for paired differences will be used. A two-tailed value of $p < 0.05$ will be considered statistically significant.

ETHICS AND DISSEMINATION

This investigator-initiated, randomised, double-blind trial has the potential to clarify whether it is possible to re-establish the diurnal variation of blood pressure in patients with type 1 diabetes with a non-dipping pattern of blood pressure during the night. A positive outcome for the primary end point will also enable us to study the effect on end-organ changes as myocardial hypertrophy. Previous studies have suggested positive effects of bedtime dosing of antihypertensive medications in open, unblinded studies in patients with type 2 diabetes, but double-blinded studies have not been performed and no studies at all have been carried out in patients with type 1 diabetes. By studying the selected patients with CAN but without simultaneous diabetic nephropathy it is possible to evaluate the effect of nocturnal antihypertensive treatment in patients with autonomic CAN alone.

A positive outcome for the primary end point of the trial may pave the way for dosing antihypertensive medication at bedtime. However, larger trials with longer intervention periods are required to study the effects of such medication on hard clinical outcomes.

The potential side effects and risks will be minimised by close measurements of 24 h blood pressure and monitoring of kidney function during the study.

The potential disadvantages, including expense of time, potential adverse events and discomfort related to blood pressure measurements and study visits are expected to be overshadowed by the knowledge and possible clinical importance that the trial outcome will produce.

The results of the study will be presented at national and international scientific meetings and publication will be submitted to peer-reviewed journals.

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REFERENCES

- Spallone V, Maiello MR, Cicconetti E, *et al.* Factors determining the 24-h blood pressure profile in normotensive patients with type 1 and type 2 diabetes. *J Hum Hypertens* 2001;15:239–46.
- Taskiran M, Rasmussen V, Rasmussen B, *et al.* Left ventricular dysfunction in normotensive type 1 diabetic patients: the impact of autonomic neuropathy. *Diabet Med* 2004;21:524–30.
- Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007;115:387–97.
- Cardoso CR, Leite NC, Freitas L, *et al.* Pattern of 24-hour ambulatory blood pressure monitoring in type 2 diabetic patients with cardiovascular dysautonomy. *Hypertens Res* 2008;31:865–72.
- Hornung RS, Mahler RF, Raftery EB. Ambulatory blood pressure and heart rate in diabetic patients: an assessment of autonomic function. *Diabet Med* 1989;6:579–85.
- Monteagudo PT, Nobrega JC, Cezarini PR, *et al.* Altered blood pressure profile, autonomic neuropathy and nephropathy in insulin-dependent diabetic patients. *Eur J Endocrinol* 1996;135:683–8.
- Spallone V, Bernardi L, Ricordi L, *et al.* Relationship between the circadian rhythms of blood pressure and sympathovagal balance in diabetic autonomic neuropathy. *Diabetes* 1993;42:1745–52.
- Spallone V, Maiello MR, Morganti R, *et al.* Usefulness of ambulatory blood pressure monitoring in predicting the presence of autonomic neuropathy in type 1 diabetic patients. *J Hum Hypertens* 2007;21:381–6.
- Verdecchia P, Porcellati C, Schillaci G, *et al.* Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793–801.
- Sturrock ND, George E, Pound N, *et al.* Non-dipping circadian blood pressure and renal impairment are associated with increased mortality in diabetes mellitus. *Diabet Med* 2000;17:360364.
- Okhubo T, Hozawa A, Yamaguchi J, *et al.* Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama Study. *J Hypertens* 2002;20:2183–9.
- Brotman DJ, Davidson MB, Boumitri M, *et al.* Impaired diurnal blood pressure variation and all-cause mortality. *Am J Hypertens* 2008;21:92–7.
- Dolan E, Stanton A, Thijs L, *et al.* Superiority of ambulatory over clinic blood pressure measurements in predicting mortality: the Dublin Outcome Study. *Hypertension* 2005;46:156–61.
- Boggia J, Li Y, Thijs L, *et al.* Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet* 2007;370:1219–29.
- Mogensen UM, Jensen T, Køber L, *et al.* Cardiovascular autonomic neuropathy and subclinical cardiovascular disease in normoalbuminuric type 1 diabetic patients. *Diabetes* 2012;61:1822–30.
- Hermida RC, Ayala DE, Fernandez JR, *et al.* Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. *Hypertension* 2008;51:69–76.
- Maser RE, Mitchell BD, Vinik AI, *et al.* The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a metaanalysis. *Diabetes Care* 2003;26:1895–901.
- Kontopoulos AG, Athyros VG, Didangelos TP, *et al.* Effect of chronic quinapril administration on heart rate variability in patients with diabetic autonomic neuropathy. *Diabetes Care* 1997;20:355–61.
- Cabezas-Cerrato J, Hermida RC, Cabezas-Agricola JM, *et al.* Cardiac autonomic neuropathy, estimated cardiovascular risk, and circadian blood pressure pattern in diabetes mellitus. *Chronobiol Int* 2009;26:942–57.
- Roy TM, Peterson HR, Snider HL, *et al.* Autonomic influence on cardiovascular performance in diabetic subjects. *Am J Med* 1989;87:383–8.
- Airaksinen KEJ. Silent coronary artery disease in diabetes: a feature of autonomic neuropathy or accelerated atherosclerosis? *Diabetologia* 2001;44:259–66.
- Vinik AI, Maser RE, Mitchell BD, *et al.* Diabetic autonomic neuropathy. *Diabetes Care* 2003;26:1553–79.
- [No authors listed]. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998;41:416–23.
- Boulton AJM, Vinik AI, Arezzo JC, *et al.* Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005;28:956–62.
- Knudsen ST, Ebbelhøj E, Poulsen PL, *et al.* Targeting nocturnal hypertension in type 2 diabetes: bedtime dosing of once-daily antihypertensive drugs reduces night-time BP and 24-h BP. *Diabetologia* 2013;56:1208:486.
- Hermida RC, Ayala DE, Mojon A, *et al.* Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. *Diabetes Care* 2011;34:1270–6.

Correction

Hjortkær H, Jensen T, Kofoed K, *et al.* Nocturnal antihypertensive treatment in patients with type 1 diabetes with autonomic neuropathy and non-dipping of blood pressure during night time: protocol for a randomised, placebo-controlled, double-blind, two-way crossover study. *BMJ Open* 2014;4:e006142. The name of the first author of this paper was spelled incorrectly. This author's correct name is Henrik Øder Hjortkær.

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